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TITLE: Massage Therapy for Reducing Stress Hormones and  
Enhancing Immune Function in Breast Cancer Survivors

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13. ABSTRACT (Maximum 200 Words) The objectives of this study were to examine massage and relaxation therapy effects for women with early stages of breast cancer for 1) reducing anxiety, stress and stress hormones, 2) decreasing depressed mood and increasing serotonin (a biochemical that diminishes with depression) and 3) increasing Natural Killer cell number and cytotoxicity (immune measures that fight tumors and viruses). During the course of the three-year study, 60 women diagnosed with Stage 1 and 2 breast cancer were to be recruited and assigned to massage (n=20), relaxation (n=20) or control groups (n=20). Women in the massage and relaxation therapies were to receive 3 sessions a week for 5 weeks. On the first and last days of the 5-week period and at a follow-up period, measures were to be collected on anxiety and depression, and urine and blood samples were to be assayed for treatment effects on stress hormones and immune measures. At this point, we have screened and enrolled 56 women into the study. Women in the <u>massage therapy</u> group showed 1) reduced anxiety, 2) improved mood, 3) increased serotonin and dopamine levels, and 4) increased Natural Killer cell numbers and lymphocytes; For the <u>relaxation group</u> , findings included 1) reduced anxiety and improved mood after the first session, 2) decreased norepinephrine (catecholamine stress marker) and 3) increased NK cell cytotoxicity. These findings support the hypotheses that massage and relaxation therapies enhance mood and immune function for women with breast cancer. A follow-up study is inconclusive at this point as not enough women have been seen. We have asked for an extension of <u>one-year to complete the follow-up</u> .				
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### **3<sup>rd</sup> Year Report**

#### **Introduction**

Breast cancer ranks as the second leading cause of cancer deaths in women (American Cancer Society, 2001). Research reveals that breast cancer patients have elevated stress hormone levels (Van der Pompe, Antoni & Heijnen, 1996), reduced Natural Killer (NK) cell number (Brittenden, Heys, Ross & Eremin, 1996), and impaired NK cell cytotoxicity after surgery (Van der Pompe, Antoni, Visser & Heijnen, 1998). NK cells and NK cell activity play an important role in lysing tumor cells, as well as monitoring and striking against neoplastic (new and abnormal) growth. That chronic stress has been associated with lower NK cell activity (Cohen, Klein, Kuten, et al., 2002), and that women with breast cancer are at risk for elevated stress and reduced NK cell number and NK cell cytotoxicity levels emphasizes the need to reduce stress levels for women with breast cancer. The current study was designed to evaluate massage and relaxation therapy effects for an ethnically diverse group of women with early stages of breast cancer (Stages 1 and 2) for 1) reducing stress, or anxiety, and biochemical stress levels, 2) decreasing depressed mood and increasing serotonin (a biochemical that diminishes with depression) and, 3) increasing immune function (i.e., NK cell number, NK cytotoxicity and lymphocytes). During the course of the three-year study, 60 women diagnosed with Stage 1 or 2 breast cancer were to be recruited and assigned to a massage therapy (n=20), a relaxation therapy (n=20) or a control group (n=20). On the first and last day of the 5-week study, measures were to be collected on anxiety and depression (mood), and urine and blood samples were to be assayed for treatment effects on biochemical stress levels and immune measures.

#### **Body**

##### **Task 1**

Over the course of the three-year study we have screened and trained numerous massage therapists on the protocol developed for the breast cancer massage. We have also developed excellent relations with the breast health center on our medical campus and local support groups, where participants for the study were recruited.

## **Task 2**

Of the participants screened, we have recruited 65 women with early stages of Breast Cancer who met criteria for the study.

## **Task 3**

Of the 65 women recruited, 52 women have completed (3 are ongoing– see relaxation group) the 5-week protocol for massage (n=20), Relaxation (n=13 completed plus 3 who are ongoing) and control (n=16). Four additional women (n=2 for the relaxation and n=2 for the control group) will be starting as soon as they meet the 3-month post-chemotherapy criterion for inclusion, 5 were dropped, and 4 have not committed to start yet. The protocol also included a follow-up visit. At least two telephone attempts have been made to schedule the follow-up visits for all the women who completed the protocol and are 6-month post treatment or control. We have only completed the follow-up for 10% of the women. However, we hope that many more will respond to our mailing reminder. We applied for a no-cost extension to attempt to complete this final phase of the protocol.

## **Task 4**

Data for the baseline and last day of the study for all of the completed participants have been scored and entered into a spreadsheet. We have analyzed these data and have also entered and analyzed the biochemical assays (urine) for the massage, relaxation and control groups, and the immune measure assays (blood) for all three groups. The results from these data analyses are summarized below and presented in Table 1. The lab conducting the urine analyses has still to complete the 5-HIAA (serotonin) assays for the relaxation group, and we hope to get those data soon. Although we have some follow-up data, we have postponed the analyses until we have more data to enter and examine.

## **Participants**

Fifty-two women ( $M$  age = 53.4 yrs old,  $sd$  = 11.3) diagnosed with Stage I or II breast cancer recruited from a university cancer center or local support group participated in this study. The 52 women in the study were ethnically distributed: 60% Caucasian, 30% Hispanic and 10% Black, and lower- middle to middle-socioeconomic status ( $M$  = 2.7 on the Hollingshead two-factor index). Participants were matched on support group and age and then assigned to a massage therapy group ( $N=20$ ), relaxation group ( $N=16$ , of which 3 need to complete last day) or standard treatment control group ( $N=16$ ). The massage sessions were 30-minutes long, three times a week for 5-weeks. The relaxation therapy sessions were also 30-minutes long, and 3 times a week and consisted of progressive muscle relaxation (PMR).

## **Results**

On the first and last day of the study, the women completed two self-report questionnaires to measure their anxiety levels (STAI) and mood (POMS). In addition, they provided urine samples, to assay for biochemical stress (cortisol and catecholamines) and mood (serotonin 5HIAA) levels, and their blood was drawn to assay the immune measures (NK cell number, NK cytotoxicity and lymphocytes).

## **Data Analyses**

A Multivariate Analysis of Variance (MANOVA) test yielded a significant group effect,  $F(32,58) = 1.68$ ,  $p = .04$  for the self-report measures. An inspection of the biochemical and immune measures data revealed that these were not normally distributed. Therefore, non-parametric statistics (Wilcoxon Signed Ranks Tests) were conducted for these and are reported below. Means and standard deviations are presented in Table 1 along with the alpha levels. A summary of the results is presented in the next paragraph.

The women in the treatment groups reported reduced anxiety (STAI) and improved mood (POMS) after the first session: massage therapy STAI:  $t(19) = 5.46$ ,  $p < .0001$ ; POMS:  $t(19) = 4.02$ ,  $p = .001$  relaxation group: STAI:  $t(15) = 3.29$ ,  $p = .006$ ; POMS:  $t(15) = 2.73$ ,  $p = .016$ , respectively.

However, only the massage therapy group continued to report decreased anxiety and improved mood on the last day of the study, massage therapy: STAI:  $t(19) = 5.64, p < .0001$ ; POMS:  $t(19) = 2.33, p < .05$ . The improved mood appeared to be related to less depressed and angry mood, as these were the two POMS subscales that changed. For the biochemical measures, the massage therapy group revealed increased serotonin (5-HIAA),  $Z = 1.64, p = .05$  and dopamine levels,  $Z = 1.85, p < .05$ , which corroborates the massage group's self-report of improved mood. Interestingly, on the biochemistry measures, the relaxation therapy group is showing reduced norepinephrine (stress-related catecholamine) levels,  $Z = 1.98, p < .05$ . Although the serotonin values for the relaxation group are not in yet, we do not expect these to change because the group did not report improved mood on the last day. The control group failed to report changes in self-reports. Interestingly, although the women in the control group did not report a change in their stress or mood levels, norepinephrine (stress-related catecholamine) levels increased from the first to the last day, suggesting that they might have been more stressed by the last day of the study. The immune measures analyses revealed for 1) the massage therapy group a 12% increase in NK cell numbers and a 10% increase in lymphocytes; 2) the relaxation group revealed an 18% increase in NK cell cytotoxicity; however, the initial lymphocyte increase we attained last year is no longer significant for the relaxation group; The control group showed no change in immune response (see Table 1).

## Discussion

The immediate psychological effects for the breast cancer participants who received 5-weeks of massage or relaxation treatment included decreased anxiety and improved mood after the first session. However, only the massage therapy group reported feeling less anxious and in a better mood on the last day of the study, suggesting that massage therapy may be perceived as more effective for reducing anxiety and improving mood. The increased urinary serotonin and dopamine levels from the first to the last day of the study corroborated the massaged group's self-report data, suggesting that massage improved the women's mood, in that an increase in these biochemical levels

is associated with less depressed mood (Weiss, Demetrikopoulos, West & Bonsall, 2000).

Interestingly, although the relaxation therapy group did not report feeling less anxious on the last day of the study, their urinary norepinephrine values (stress –related catecholamines) decreased. This is encouraging and suggests that relaxation therapy has stress-reducing benefits at the biochemical level.

The critical question for this study was whether massage and/or relaxation therapies would positively impact the immune system of women with breast cancer, as has been shown for HIV. In the current study, the analyses of the immune measures from the first to the last day of the study revealed increased NK cell number and lymphocytes for the massage therapy group, and increased NK cell activity for the relaxation group. These immune measure changes support the HIV men's massage therapy finding (Ironson, Field, et al., 1996), and a recent HIV adolescent girls' massage therapy study (Diego, et al., 2001), and support the hypothesis of the current study that massage and relaxation positively impact the immune system of women with breast cancer. The increase in lymphocytes for the massage therapy group has not been previously reported and is important in that lymphocytes are precursor cells of immunological function as well as regulators and effectors of immunity. The increased NK cell activity for the relaxation group, together with the reduced anxiety and improved mood they reported after the first treatment, and their reduced norepinephrine (stress catecholamine) values from the first to the last day of the study suggest that progressive muscle relaxation therapy (like massage therapy) may be effective for attenuating psychological, biochemical and immunological symptoms associated with breast cancer. These data support our original hypothesis that massage therapy (and relaxation) improves the psychological, biochemical and immunological responses of women diagnosed with early stages of breast cancer. The longer-term effect of these therapies is unknown at this point in the study, until the follow-up visits are completed and these data analyzed.



### Recommended Changes

Our only recommended change is for a one-year no cost extension to complete the ongoing participants and the follow-up visits.

## Key Research Accomplishments

- Screened and recruited 65 women with breast cancer.
- Completed treatment protocol for 49 women (plus 3 ongoing will be completing soon for a total of  $n=52$ ), and have 4 other women who will be starting the relaxation or control group (for a total of 56 participants).
- Scored, entered and analyzed the self-report data for all completed subjects.
- Entered and analyzed the biochemical and immune measures' data.
- Comparison of 1<sup>st</sup> versus last day's measures for women in the massage therapy group and relaxation therapy groups support our hypotheses that these therapies:
  - a) decreased stress (or anxiety) and improved mood
  - b) affected the biochemistry of the breast cancer participants in a positive manner, including increasing urinary serotonin and dopamine levels for the massage group, and decreasing norepinephrine for the relaxation therapy group.
  - c) positively affected the immune system of the participants, including increasing Natural Killer cell numbers and lymphocytes for the massage group and increasing Natural Killer cell activity for the relaxation group.

## **Reportable Outcomes**

### **Conference Presentations**

Ironson, G., (2002). "Impact of Massage on Biology and Well-Being in Cancer and Aids Patients." Paper to be presented August 14, 2002 at the Second Annual DOD Population Health and Health Promotion Conference, Baltimore, MD.

Ironson, G. (2002). "Massage Therapy for Reducing Stress Hormones and Enhancing Immune Function in Breast Cancer Survivors (BC980215). Paper to be presented September 2002 at the DOD Era of Hope Conference.

### **Manuscripts:**

Hernandez-Reif, M., Ironson, G., Field, T., Hurley, J., Katz, G., Diego, M., Weiss, S., Fletcher, M., Schanberg, S., & Kuhn, C. (2001). Breast Cancer patients have improved immune and neuroendocrine functions following massage therapy. (in review with Psycho-Oncology).

Hernandez-Reif, M., Field, T., Beutler, J., Ironson, G., Hurley, J., Fletcher, M., Schanberg, S., & Kuhn, C. (2001). Breast Cancer patients show improved mood, reduced norepinephrine and increased NK cell cytotoxicity following progressive muscle relaxation (manuscript in preparation).

### **Funding applied for based on work supported by this award:**

1. Ovarian Cancer, Massage Therapy and Group Therapy, IDEA Award, DOD.
2. Prostate Cancer, Massage Therapy and Group Therapy, IDEA Award, DOD.
3. Breast Cancer, Massage vs Sham Massage, IDEA Award, DOD.

## **Conclusions**

The study's findings imply that breast cancer patients may benefit from massage and relaxation therapies. Specifically, the findings revealed that massage therapy was associated with 1) reduced anxiety and depressed mood, 2) increased urinary serotonin and dopamine values and 3) increased lymphocytes and NK cell numbers from the first to the last day of the study. These findings support the hypothesis that massage therapy has a positive impact on the psychological, biochemical and immunological functions of women with breast cancer. The findings were also positive for women with breast cancer who received progressive muscle relaxation therapy, including 1) reduced anxiety and depressed mood after the first session, 2) reduced norepinephrine (stress-related catecholamine)

values, and 3) increased NK cell cytotoxicity from the first to the last day of the study. Because progressive muscle relaxation can be conducted at home by listening to an audiotape, this suggests that it can be a cost-effective intervention for women with breast cancer.

### **“So What”**

The findings from this 3-year study showed that women with early stages of breast cancer benefited from massage and relaxation therapies. Findings associated with these therapies included reduced anxiety, improved mood, and biochemical and immunological benefits. Because these therapies proved to be therapeutic and are non-invasive, pose no side effects or interactions with medications, they should be considered as adjunct therapies for women with breast cancer. Although most women will probably prefer massage therapy, it is not covered by most insurance carriers. Perhaps the significant other, friend or family member of the breast cancer patient could be trained to conduct the massage protocol, as we have in other studies (e.g., depressed pregnant women), to make massage therapy more cost-effective. One advantage to relaxation therapy is that it is cost-effective in that women can conduct relaxation sessions at home by listening to an audiotape. The findings also support that massage and relaxation therapies were well received by an ethnically diverse group of women with breast cancer, suggesting the generalizability of the therapies across at least three different races. In summary, massage and relaxation therapies when offered in conjunction with standard care, may improve the quality of life of women undergoing the stressors of living with a life-threatening disease. Moreover, in that these therapies positively impacted so many different aspects of functioning (psychological, biochemical and immunological), warrants further study of massage and relaxation therapies for breast cancer survivors.

## References

American Cancer Society, Inc (2001). Breast Cancer Facts and Figures 2001-2002. 01-50M-No. 8610.01-R, Atlanta, Ga.

Brittenden J, Heys S, Ross J, Eremin O. (1996). Natural killer cells and cancer. Cancer, 77, 1226-43.

Cohen, M., Klein, E., Kuten, A., Fried, G., Zinder, O., & Pollack, S. (2002). Increased emotional distress in daughters of breast cancer patients is associated with decreased natural cytotoxic activity, elevated levels of stress hormones and decreased secretion of Th1 cytokines. International Journal of Cancer, 100, 347-354.

Diego, M., Field, T., & Hernandez-Reif, M., Friedman, L., & Shaw, K. (2001). HIV adolescents show improved immune function following massage therapy. International Journal of Neuroscience, 106, 35-45.

Ironson G, Field T, Scafidi F, Kumar M, et al. (1996). Massage therapy is associated with enhancement of the immune system's cytotoxic capacity. International Journal of Neuroscience, 84, 205-17.

Van der Pompe, G., Antoni, M., & Heijnen, C. (1996). Elevated basal cortisol levels and attenuated ACTH and cortisol responses to a behavioral challenge in women with metastatic breast cancer. Psychoneuroendocrinology, 21, 361-374.

Van der Pompe G, Antoni M, Visser A, Heijnen C. (1998). Effect of mild acute stress on immune cell distribution and natural killer cell activity in breast cancer patients. Biological Psychology, 48, 21-35.

Weiss J, Demetrikopoulos M, West C, Bonsall R. (2000) An hypothesis linking the noradrenergic and dopaminergic symptoms in depression (in press).

Table 1. Means (standard deviations in parentheses) for the massage therapy, relaxation therapy and control group for First and Last Days (Pre and Post treatment or control period).

Variables	Massage		Relaxation		Control	
	FIRST Pre/Post	LAST Pre/Post	FIRST Pre/Post	LAST Pre/Post	FIRST Pre/post	LAST Pre/post
<u>Self-reports †</u>						
Anxiety (STAI)	37(14) <sub>a</sub> /27(13) <sub>b</sub> **	35(10) <sub>a</sub> /25(8) <sub>b</sub> **	35(14) <sub>a</sub> /29(10) <sub>b</sub> *	35(11) <sub>a</sub> /30(12) <sub>a</sub>	32(9) <sub>a</sub> /30(6) <sub>a</sub>	35(12) <sub>a</sub> /32(9) <sub>a</sub>
<u>Mood (POMS)</u>						
Depression	12(11) <sub>a</sub> /3(3) <sub>b</sub> **	7(7) <sub>b</sub> */3(4) <sub>b</sub> *	11(14) <sub>a</sub> /7(12) <sub>b</sub> *	10(15) <sub>a</sub> /15(30) <sub>a</sub>	4(4) <sub>a</sub> /3(3) <sub>a</sub>	6(7) <sub>a</sub> /5(7) <sub>a</sub>
Anger	10(8) <sub>a</sub> /2(2) <sub>b</sub> **	3(3) <sub>b</sub> /2(2) <sub>b</sub>	7(6) <sub>a</sub> /3(5) <sub>b</sub> **	5(7) <sub>a</sub> /4(6) <sub>a</sub>	5(5) <sub>a</sub> /5(4) <sub>a</sub>	3(4) <sub>a</sub> /4(5) <sub>a</sub>
<u>Biochemical</u>						
<u>Stress related</u>						
Cortisol †	156 (47) <sub>a</sub>	173 (77) <sub>a</sub>	158 (64) <sub>a</sub>	127(15) <sub>a</sub>	185(74) <sub>a</sub>	179 (72) <sub>a</sub>
Norepinephrine	44(32)	54(16) <sub>a</sub>	51(33) <sub>a</sub>	39 (20) <sub>b</sub>	42(25) <sub>a</sub>	73(33) <sub>b</sub>
<u>Mood related</u>						
5HIAA †	2114 (1369) <sub>a</sub>	3391 (2064) <sub>b</sub> *	249(110) <sub>a</sub>	201(127) <sub>b</sub>	3395 (2004) <sub>a</sub>	3456 (1775) <sub>a</sub>
Dopamine ‡	258 (110) <sub>a</sub>	325 (80) <sub>b</sub>			224 (150) <sub>a</sub>	281(77) <sub>a</sub>
<u>Immune Measures ‡</u>						
NK Cell	235(129) <sub>a</sub>	263(95) <sub>b</sub> *	337(147) <sub>a</sub>	350(226) <sub>a</sub>	254(90) <sub>a</sub>	236(67) <sub>a</sub>
NK Activity	27(13) <sub>a</sub>	29(13) <sub>a</sub>	27(9) <sub>a</sub>	32(14) <sub>b</sub> *	29(13) <sub>a</sub>	29(16) <sub>a</sub>
Lymphocytes	29(4) <sub>a</sub>	32(7) <sub>b</sub> *	30(9) <sub>a</sub>	31(10) <sub>a</sub>	30(8) <sub>a</sub>	30(7) <sub>a</sub>

† Lower scores are optimal; ‡ Higher scores are optimal. Different letter subscripts indicate significant differences between adjacent means at the \*  $p < .05$ , \*\*  $p < .01$

## **Bibliography**

See Reportable Outcomes for papers in review and abstract presentations

### **Personnel Receiving Pay**

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Therapists and student: Julia Beutler, Larissa Feijo, Karla Gil, Amparo Roca, Maria Perez.  
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